

Perlman, Robert L. 2008

Dr. Robert L. Perlman Oral History 2008

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NCI Laboratory of Molecular Biology

Oral History Project

Interview with Dr. Robert L. Perlman

Conducted on November 7, 2008, by Jason Gart

JG: My name is Jason Gart and I am a senior historian at History Associates Incorporated in Rockville, Maryland. Today's date is November 7, 2008, and we are in the offices of the National Institutes of Health in Bethesda, Maryland. Please state your full name and also spell it.

RP: My name is Robert Perlman, P-E-R-L-M-A-N.

JG: Terrific. I just want to briefly describe the interview scope. Established in 1970, the Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, commonly known as LMB has among its ten groups four members of the National Academy of Sciences. LMB has trained many other prominent scientists and its research has contributed both to basic science and to novel applied cancer treatments. LMB has initiated this oral history program to capture recollections of prominent scientists currently or formerly associated with the laboratory. You were born in Chicago?

RP: Yes, I was.

JG: In August 1938? What were some of your interests as a child?

RP: Sports probably. I grew up as a Cubs fan.

JG: Did you?

RP: Yes. I enjoyed playing as well as watching. I suppose other than sports I was probably a nerd. I was pretty bookish and always interested in school work kinds of things, largely math and science, but more broadly. I grew up in a Jewish family and in my childhood at various points my Jewish identity was important to me. That has waxed and waned and has currently disappeared completely but I remember as a child at one point thinking that maybe I would be a Rabbi when I grew up so that was also an important part of my life.

JG: What did your parents do for a living?

RP: My father was a physician. He was a surgeon on the faculty at the University of Chicago. My mother had been a newspaper reporter but she stopped working when my brother was born and so was a homemaker throughout my childhood.

JG: Did your high school teachers—

RP: Well and I guess I should say that since my father was on the faculty at the University of Chicago we grew up in Hyde Park which has now become prominent. I went to the Lab School [University of Chicago Laboratory Schools] where the Obama children have been going. I sort of grew up in that university community which I think was an important influence on me.

JG: Speak about some of your high school teachers. Were there any that were especially influential?

RP: Wow. I had a brief episode transferring to the local public high school because I wanted to hang out with the kids in my neighborhood and when I was there there was a Latin teacher, Miss Gillogly, who was just terrific. We didn't use "Ms." in those days. I loved learning Latin and she was a very important in stimulating this interest. It is sort of a regret that I never learned a living foreign language but I was reasonably good at reading and translating Latin when I was a teenager. I owe that very much to her.

JG: Did your father steer you towards medicine or the sciences or was it something that was left to you?

RP: It was certainly nothing overt. But I think in the cultural milieu which I grew up becoming a doctor was sort of one of the things that was expected of a young boy.

JG: How about—

RP: Actually, when I was born my original middle name was Galen and my mother, who I don't think was very psychologically inclined, always maintained that they named me Galen because they thought it was a pretty name and it had nothing to do with the idea that they might want me to become a physician. I have always found that rather amusing. When I was a teenager I was very attached to my grandfather and when he died, I changed my middle name to Louis in memory of him. So I am no longer Robert Galen. So there was some, I won't say pressure, but some expectation I suppose that I might become a doctor.

JG: What did your grandfather do?

RP: He was an immigrant who was a peddler and then opened what was called in those days a dry goods store and selling clothing to steel workers outside of Gary, Indiana.

JG: So you attended the University of Chicago?

RP: Yes.

JG: Walk me through your degrees leading up to your medical school degree in 1961. You got an A.B. in 1957 and then an S.B. in 1958?

RP: Right. So this was at the tail end of the so-called [Robert Maynard] Hutchins era at the University of Chicago which really focused on general education or liberal education. There weren't majors. There was a set of courses we all studied—natural sciences, social sciences, and humanities, and it was just a marvelous education that I am very pleased to have had. I graduated in 1957 and I started medical school then in the autumn of 1957. The S. B. was something that one could pick up because they let you count the science courses that you had during the first year of medical school to then satisfy the requirements for the other bachelors degree. It was sort of a meaningless degree but at the time it seemed worth doing.

JG: Let me stop you there. So for your A.B. it was basically just a liberal education with an emphasis on the sciences. At that time did you know that you wanted to go to medical school or were you still looking at other career paths?

RP: It is hard to reconstruct. I think I often . . . Well after briefly thinking maybe I would become a philosopher, and deciding that was not for me, I waived between going to medical school and going to graduate school in one of the biological sciences. What is hard to reconstruct is that there was a draft in those days and staying in school was essential in order to avoid being drafted so I did not have the luxury of taking time off after college. One had to keep going on in school or one would get drafted. I can't reconstruct whether at that point in my life that being sure that I was safe from the draft was an important consideration but it certainly became important later. I guess by the third year in college I was taking biology courses but most of the biology students were themselves pre-med so I was part of a group. Most of my friends and classmates were headed toward medical school so I think I was very much in that mindset.

JG: Okay, looking at it in another way, what really interested you about medical school? What was the attraction?

RP: The attraction was very much research. Because of the educational program at the University of Chicago I wound up graduating from college very young. I was nineteen or twenty, or whatever it was. In retrospect I probably was not mature enough to be a medical student and have the responsibility of taking care of patients. I had not developed to that point yet. So the science laboratory side of medicine was much more attractive to me.

JG: Talk a little bit about that training. This would have been 1959 or 1960. How did they train young doctors?

RP: Well, the first two years in those days were pretty standard, basic science courses with a lot of laboratory work involved in the courses. So not just in gross anatomy, where I dissected a cadaver, but the biochemistry had a laboratory where you did all kinds of biochemical assays and we did lots of physiological studies with dogs in physiology and pharmacology. It was a heavy course load, a heavy laboratory load, and very little patient contact. There was one course in the first year where each of us were assigned to a pregnant woman and we met with her every time she came to the hospital for prenatal care and then saw her in her delivery and made a home visit afterwards. It was a very nice program but it was a very small part of the curriculum.

The clinical years was very much . . . I suppose what you would call an apprentice model. It was a relatively small faculty. There were small teams of a faculty member and a resident and an intern and a medical student and you spent your time taking histories of patients and doing physical exams and then presenting those to the intern and then to the resident and then to the attending physician and you learned very much from the modeling that you got from the interacting with the people who were more experienced than you.

JG: You graduate in 1961?

RP: Yes.

JG: What are your options? You decide to go on and get a Ph.D. in biochemistry. What took you there?

RP: Well a couple of things. One, is again I was really young and I think I wasn't ready to be an intern. But while I was in medical school I became very heavily influenced by Albert Dorfman who was a pediatrician and biochemist professor. That is D-O-R-F-M-A-N. He was a professor of pediatrics and of biochemistry and was very much a role model for me and very, very influential in my career. He encouraged me to take time after medical school and work with him and get my Ph.D. in biochemistry under his supervision.

JG: Where was Dr. Dorfman trained and what type of scientist was he?

RP: He had also been educated at the University of Chicago. His clinical work was in rheumatic fever and he took care of kids. He was director of a rheumatic fever sanitarium, the La Rabida Jackson Park Sanitarium at the time. His science research was related to what in those days was called connective tissue or mucopolysaccharides. Now they are known as proteoglycans. My doctoral dissertation had to do with the biosynthesis of chondroitin sulfate, which is one of the proteoglycans, found prominently in cartilages, so the studies we did were with embryonic chick cartilage looking at incorporation of radioactive precursors into the large polymer of chondroitin sulfate.

JG: At this point, and maybe this is prior to your Ph.D., but have you given any consideration to pursuing surgery like your father?

RP: No, that did not interest me at all.

JG: Why not?

RP: Maybe no good reason but I did not like that kind of physical approach to medicine. The kinds of medicine that I found more interesting were more the diagnostic and therapeutic challenges and I did finally really enjoy taking care of patients. But I don't know, the surgery just never interested me at all.

JG: You go to Bellevue Hospital—

RP: Yes.

JG: —and do your internship and residency there?

RP: Yes.

JG: Talk about that process and how that impacted your career. Who were some of your mentors?

RP: Well I have always been torn, and I should have mentioned it earlier, because it was important in college, too. I have always been torn between the science side of medicine and a more public health, social action sort of career. When I was getting my Ph.D., and then applying for internships in pediatrics, the two places that I was considering were Boston Children's Hospital and Bellevue [Hospital Center]. Boston Children's Hospital would have been the more strictly academic approach to medicine and I chose to go to Bellevue because it was a big city hospital taking care of the poor and impoverished community. I thought this was a way of embracing some of the other values of medicine that I had not really done anything about while I was in medical school. I was very much attracted to working in the Bellevue Hospital environment.

JG: What was it like in the early 1960s to be at Bellevue? It is kind of a famous hospital.

RP: Yes, it is. Now there is a new building; this was their old building from the nineteenth century. I remember that the first day I was there I was walking in one of the tunnels and there was a cockroach and I thought it was a rat. It was the biggest thing I had ever seen. [Laughs]

Because it was understaffed, and I guess this was a part of the medical model in those days, as interns we had enormous amounts of autonomy and responsibility. We were on-call all the time. We were there sort of on the front line and we developed the mentality that the buck stopped with you and the people who had no place else to go would be sent to Bellevue and it was our job to do our best. There was a wonderful *esprit* among the house staff there.

These were sick people with few options. It was a large Spanish speaking community and I did make an effort to at least learn enough medical Spanish that I could talk to the mothers about their children. I was never fluent but I could at least ask what brought them to the hospital and whether the kid had a fever and things of that sort.

JG: Describe some of your colleagues and your other mentors there.

RP: Well there were a couple of people who were important. Most important was probably Charles D. May, who was the professor of pediatrics there at the time, a general pediatrician interested in nutrition. But he too was sort of—I would not say a social rebel—but he came to Bellevue because he had written an article in *The Journal of Medical Education* about the role of drug companies in influencing prescribing behavior by physicians. It was calling "Selling Drugs by 'Educating' Physicians" or something like that. It was one of the first, now it is sort of common knowledge, but this is one of the first exposés of how the pharmaceutical industry was influencing the practice of medicine. He had been at Columbia [University] and I have a feeling that having written this article he got drummed out of a more prestigious place and wound up at Bellevue. I worked with him and was very, very attached to him.

JG: We skipped over it but how did you come to be interested in pediatrics?

RP: Well that really came from Albert Dorfman who was my mentor in Chicago and I think I became a pediatrician because he was a pediatrician and he was so much a model for me. I think before I got close to him I would have chosen internal medicine rather than pediatrics.

JG: Compare New York City to Chicago during this period.

RP: Well certainly the medical environments were totally different. I mean Chicago was a very academically oriented program and Bellevue was this large community based program. I felt I really had led a sheltered life at Chicago and was now exposed to the real world. So that was a very interesting challenge. In terms of the cities, as an intern, we didn't do much. We were on call every other night. My now wife, but my then girlfriend, we were living together before that became as common as it is now, but she would say that when I came home from work she would want to talk to me before she gave me dinner because she knew as soon as I ate I would fall asleep. The only way to have any time together was to keep me hungry. [Laughs]

Just this summer, she was a New Yorker, and we were in New York, and she wanted to go to Yankee Stadium to see a Yankees game before they tore down the old stadium and I realized that in the two years that I was in New York I never went to a baseball game. Either I was working or sleeping and yet it was a wonderful two years. I learned a lot and have very good feelings about it but I can't say that I got to explore much of New York.

JG: What brought you to NIH in 1965?

RP: Well that is totally the draft. So you probably know about the Berry Plan. I was in the Berry Plan and fortunate enough to get into the U.S. Public Health Service Commissioned Corps. I really don't know what I would have done if I hadn't been able to get into the Public Health Service. I think it would have been very difficult for me to go into one of the military services. We have relatives in Canada, very distant relatives, who I really didn't know, but during that era they wrote to my parents and said that if my brother or I wanted asylum they would be happy for us to come to Canada and stay with them. Whether I would have done that as an alternative to going into the Army I don't know because I fortunately did not have to face that. One of my colleagues at Bellevue got into a lot of trouble because—I don't remember exactly the details—he escaped the draft. I was in a sense enormously fortunate that I did not have to face that because I was able to get this commission in the Public Health Service.

JG: I assume that there were hundreds of people trying to get into the program.

RP: Yes. I don't know the numbers. It was very competitive and I was very fortunate to get it. I think it was at least in part due to Albert Dorfman from Chicago and Saul Krugman who was the chairman of the Pediatrics Department at Bellevue. I don't remember the details but I think it was their support that enabled me to get into the Public Health Service. At that point I imagined a career that would have been more clinical and public health oriented having just been at Bellevue. When I got into the Public Health Service the unit to which I was assigned was the Office of International Research and that was what I wanted to do was to go overseas. They had programs all around the country and I was supposed to go to Ghana. Just before I was to be coming to NIH and having that assignment there was a revolution in the country and a civil war and the NIH Program was abandoned and so I had no place to go. There was talk of a program in Egypt that they would send me to but they realized that I was Jewish and I would not have been accepted.

So had things worked out differently, and I don't know how different I am from other people, but I think the way my career developed was very much a product of chance. It is not as though I set out when I was in college or medical school to wind up doing what I am doing now. As I say, if there had not been the civil war in Ghana I would have gone off and studied sickle cell disease in Ghana and had a very different kind of career and at the time that is what I wanted to do. The options in the Office of International Research disappeared in the spring of 1965 just before I was supposed to start my Public Health Service Commission and somehow, and I do not even understand how it happened, I was able to come down to NIH and interview for positions as a staff associate on the NIH campus because there were no international opportunities for me.

JG: Describe Bethesda and Washington in 1965. It is the South?

RP: Oh, yes. It was very much the South, very much small town. It was sort of culture shock. We did not like it at all. We lived in the District in Glover Park just north of Georgetown. We were some of the very few NIH people who lived in the District. Everybody else lived out here, but this was so suburban, and all the garden apartments that were prevalent then, we went and we looked at some of them, we thought this is not for us. So we lived in the District and that was a much better place for us. I mean I am amazed at the transformation of Bethesda, but Washington was also a sort of sleepy backwards town. The Government was much smaller then. This is before the Kennedy Center was built so the cultural life in the city was much less than it is now. My wife is from New York as I say and having lived our lives in Chicago and New York this was not the kind of place we imagined staying.

JG: You become a staff associate in the Clinical Endocrinology Branch?

RP: Yes.

JG: Who do you work for?

RP: I worked with Harold Edelhoch—E-D-E-L-H-O-C-H. He was a physical chemist. The clinical endocrinology branch had a very large thyroid group and he studied the physical chemistry of thyroglobulin, the main protein in the thyroid. I came to be a staff associate in his laboratory, not because endocrinology or thyroid research was my passion, but I had to find a place to go at the last minute and he had an opening and it seemed interesting. I figured I would learn something, and I would stay out of Vietnam, and so I took it.

JG: What was his research agenda and what were your responsibilities?

RP: Well, I and the other people of my generation who came here, were so fortunate because it was basically a post doctoral fellowship. I did research all day long and it was a research environment. It was just like working in a university laboratory. I was a Commissioned Officer in the Public Health Service, but in those days, at least on the NIH campus, that really had little impact.

I notice today that the officers of the Public Health Service now wear uniforms on campus but when I was here we did not. It used to be amusing because we would get memos from the Surgeon General twice a year telling us when it was time to change into our summer uniform or our winter uniform and we would laugh about it because we wore civilian clothes and, of course, there was not any of this security here. It was a research institute and we were just enormously fortunate to be able to come and work in that environment. We were known as the "Yellow Berets." You have heard that I am sure?

JG: No, I have not.

RP: As opposed to the Green Berets. We were the ones who were too chicken to fight.

JG: Had you had any interaction with NIH before you arrive here? How did your mentors at Bellevue or the University of Chicago describe it?

RP: I knew nothing about it, really. When I was a graduate student I had an NIH Fellowship so I knew about the institution. But I had never visited here until the spring of 1965 when I came down to interview for the position that I got. I had no idea what to expect. It was not something that people talked about.

JG: Describe the techniques of biology in the mid-1960s? I assume it was a lot different than today. You did not have the computing power and the—

RP: There were no computers. We would type our manuscripts and we would literally cut and paste them. I remember having the scissors and you would type a piece of paper and you would cut out sentences and paste them in the order which you wanted them. It was very amusing. I remember when we got the first Wang calculator. It just seemed like a miracle device. There weren't all of the kits that are now available from the chemical supply companies to do assays where all the agents are prepackaged and you have kits to do your experiments. If you wanted reagents you would purify them yourself.

I think the lab groups were probably on average smaller. The pace was slower. The techniques of protein purification, which were probably primitive in those days, but it was column chromatography to purify proteins using analytical ultracentrifuges to look at the purity of the protein that you had and things of that sort. A lot of work with radioisotope incorporation of proteins was the kind of work that I did when I was a graduate student. This was before the techniques of molecular biology and genetics, these were classic biochemical techniques, chromatography and electrophoresis, things of that sort.

JG: Actually, that is a good point. When did you first learn about the discovery of the double helix structure and did that impact you at the time?

RP: I am sure we learned about it in college biology and everybody thought it was very exciting. I do not think people quite knew what to make of it. But, yes, that was an exciting discovery but it did not immediately change research or at least not the research that I was exposed to.

JG: When do you meet Ira Pastan?

RP: I came here in 1965 and Ira was also in the Clinical Endocrinology Branch and so his lab was down the hall from where Harold Edelhoch's lab was. I met him when I first came here which would have been July of 1965. I remember going to a party at the Pastans' house that they had for the new associates, or maybe for the whole Clinical Endocrinology Branch, to welcome new people probably that summer of 1965.

JG: What were your first impressions?

RP: I was impressed that they lived much more elegantly than the way I had always lived as a student and as an intern. [Laughs]

One of the things that I was exposed to when I came to NIH was journal clubs. We did have a journal club at Chicago but I don't remember it as a particularly intense experience. And, of course, I did not participate in anything like that when I was at Bellevue. There were weekly journal clubs in the CEB [Clinical Endocrinology Branch] as it was called and people would present papers and really dissect them and criticize them and tear them apart in a way and it was a wonderful learning experience for new people entering into the field like myself. I remember on the one hand being impressed at Ira's critical skill in doing that. I also remember feeling sort of depressed that research was impossible because there were flaws in everything and it seemed almost futile that you could not really do experiments that would satisfy critics. It was a stimulating environment in which to be.

JG: Walk me through some of the research that you are conducting during the mid-1960s. What are some of the things that you are interested in?

RP: My responsibility really was working with Harold Edelhoch and he was interested in the way thyroxine and *triiodothyronine*, the thyroid hormones, get formed within the thyroglobulin molecule. We would isolate thyroglobulin and then chemically iodinate it and try to understand the mechanisms and the regulation of how the hormones were formed in the protein. We also did physical chemical studies on the protein to understand its structure from the relatively crude techniques, by today's standards, that were then available. We used fluorescence techniques to try and understand how rigid and flexible the protein was. You could, through a technique of fluorescence energy transfer, look at distances between amino acids and different parts of the molecule. We were able to do physical chemical studies of thyroglobulin. It was very much a protein physical chemistry laboratory and that was the research that I did with Harold and he was very generous about letting me sort of look around to see what else I was interested in and pursue other things in my spare time. My primary responsibility was the work that he was doing.

JG: Do you begin to publish at this point?

RP: Yes. You know I was thinking in preparation for this I should have gone back and looked at my CV or looked at my old publications. I did not do that. You probably have. [Laughs]

JG: Yes, I did. It is in my briefcase over there. [Laughs]

RP: You know I think I had one publication from my Ph.D. dissertation and then my next publications would have been with Harold and they were on the physical chemistry of thyroglobulin. I think probably—I can't reconstruct exactly what we were doing—that I came in to some research in progress and just sort of plugged in and continued to do that. Over the next two or three years we probably published a half a dozen papers or worked on some together on thyroglobulin. I am just guessing, but if I came here in July 1965, I assume that by 1966 we began to have publications together.

JG: You begin to take an interest in cyclic AMP and then also *E. coli*?

RP: It is so hard to reconstruct this. Of course, cyclic AMP was a very hot subject in endocrinology because it was being recognized as a so-called second messenger in hormone action. Among the other places it was important was the thyroid gland because the thyroid stimulated hormone activated adenyl cyclase and elevated cyclic AMP levels of the thyroid and that was part of the mechanism of action. It is widely important in hormone action and so although I was not doing any work immediately on cyclic AMP it was something that was always discussed at journal clubs and informal conversations because it was a hot subject in endocrinology. Sometime around then, I don't know if it was 1967 or so, Earl W. Sutherland, Jr., who ultimately won the Nobel Prize for discovering cyclic AMP, came and gave a talk and it was sort of inspiring to hear how important this molecule seemed to be at the time.

JG: By 1969 you had been at NIH for four years. How did you see your career progressing?

RP: Well, when I came here in 1965 I came with the two year commission and I was not real comfortable living in the South. There was a lot I did not like about NIH and being a government employee.

JG: Like what?

RP: The Hatch Act on expressing political opinions. When I came down here I really thought that I would stay here for two years, go back to New York or someplace else to finish my residency, and pursue a clinical career. After I got here I was enjoying the research and this was a time when NIH was growing, so it was possible for me to stay on, and I ultimately was able to get a permanent position. After two or three years, I would assume as soon as I could, but I do not remember, I transferred from the Public Health Service to the civil service side. I did not like the idea of even being that close to the uniformed services. [Laughs]

JG: At this point Ira's lab is beginning to form in 1970?

RP: Ira and I must have started collaborating around 1967. Whether it was before I finished my two years, I don't remember exactly how that worked. I know we were excited about cyclic AMP. We had read this paper by Makman and Sutherland which I think was published in 1965 that described cyclic AMP and *E-coli* and described that its level increased when *E-coli* ran out of glucose and were in so-called stationery phase. I just remember talking about this with him and I would guess it was around 1967. We were sort of thinking about if there was some way to study this. We wondered about studying the role of cyclic AMP in bacterial sporulation because when bacteria run out of energy and go into stationery phase some species of bacteria form spores and we thought maybe cyclic AMP would be involved in that and maybe we should study sporulation.

We did not do that. Somehow we were attracted to looking at gene expression because we knew about what was in those days called catabolite repression, the idea that when cells were growing on glucose they did not express the genes that were necessary to use other carbon sources like lactose or galactose and so there was this correlation at least from the literature that when cells were growing on glucose they had low levels of cyclic AMP and they did not express these genes and when they ran out of glucose they had high levels of cyclic AMP and they did express the genes. We decided we would try to study that.

I would guess that was sometime around mid- to late 1967 because I think our first publications were in 1968 and I think the lag from doing the research to publishing was shorter then it is now. I would guess that was the time schedule but I don't really know.

JG: What type of scientist is Dr. Pastan?

RP: I think what impressed me was sort of his enthusiasm and I think we both had it but it was probably infectious and I got a lot of it from him. It was a time when we couldn't wait to do the experiments and then talk about them and then plan the next one. It was just a very heady exciting time. We would do experiments during the day and then go home and after dinner we would talk on the phone—what the results were and how to understand them and what we should do the next day. My wife said that we were like two teenage girls who wanted to talk on the phone all day long. It was just a very exciting and intense collaboration.

JG: I guess it could be difficult to collaborate with other researchers and other scientists. Do you remember a specific "Aha" moment in the research?

RP: The first results of showing that cyclic AMP did increase the synthesis of β -galactosidase synthesis was as much of an "Aha" moment as I have ever had. We worried about how cyclic AMP was going to get into the cells, whether the experiments were going to work, but we just put it in, and it did work, and that was enormously exciting and then much of the rest of the work was more carefully documenting it and then trying to work out the mechanisms by which it acted. But the original phenomenon was what was exciting.

This was in a sense the fusion of several topics that seemed very exciting at the moment because there was cyclic AMP on the one hand and the *lac* operon which is something that [Francois] Jacob and [Jacques] Monod had won the Nobel Prize for elucidating the regulation of these enzymes and so to put them together made us feel that we were right at the epicenter of important science.

JG: You mentioned several successes. How about a failure or difficulty? Do you have an example of something that did not work out the way you thought it would?

RP: I think some of the experiments were difficult because we did not have good enough techniques to study the process—

JG: These are the assays?

RP: Yes. One of the issues that we were very interested in was did cyclic AMP affect transcription, RNA synthesis, or translation. We ultimately worked out ways of studying that directly but initially you tried to do experiments by adding inhibitors of one process or another and then seeing whether you could see residual effects and that was not a productive pathway. The path that really became more productive was to develop cell free *in vitro* ways of studying transcription directly.

No, I think there were relatively few research setbacks. I think all of that went very smoothly. There were publication setbacks because our initial papers were rejected and we were very despondent about that. It took a while to—

JG: They were rejected because they did not believe that you actually got the results?

RP: I don't know if I ever saved the rejection letters or what was said but this was a radical new idea and people who had been in the field, there were people who studied this phenomenon of catabolite repression for a long time, and the model that they had was just completely the opposite of what we had. Because of the work of Jacob and Monod the idea was that genes were regulated by repression. Genes were turned off by repressors. The whole concept of catabolite repression was that when cells were growing on glucose there was some unknown molecules that accumulated that repressed the expression of these genes.

It turned out that the cyclic AMP was an activator of the gene, so you weren't relieving the repression you were actually activating. The old model was that when the cells were growing on glucose there were these hypothetical repressors. When the cells ran out of glucose these repressors were degraded and decreased in concentration and then the gene expression was because of de-repression. What we were saying was "No, it is induction and activation of transcription," and that was just contrary to the prevailing models of how genes were regulated. I think there was reluctance to accept that. I don't think anybody doubted the results because they were robust and clear. I think what they questioned was the interpretation.

JG: Walk through to 1971 when you leave NIH.

RP: Ira and I began collaborating in 1967 or 1968. This was after I finished my two years in the Public Health Service and I got my own laboratory and became a staff scientist or whatever the title was at the time with my own module that I was very proud of.

JG: You hired technicians and postdocs?

RP: I had a technician and had occasional research associates but mostly it was myself and a technician. Ira had a larger group. We continued to collaborate and it was the most exciting scientific time in my life. I think the Nixon presidency made being in Washington and being a government employee even less pleasant than being here under [President Lyndon] Johnson. I was very opposed to the war in Vietnam and felt very uncomfortable being here and I think I did always imagine an academic career at a university rather than a research institute.

I think at some point, I can't say exactly when, I really decided that I didn't want to spend my adult life working at NIH. But for the time being it was very exciting, the work was going well, it was wonderful. We collaborated and then I guess it was 1970 Ira was offered a position at NCI and he left Building 10.

JG: This was the endocrinology branch?

RP: He left the endocrinology branch and he offered me a position in his new laboratory and I thought a lot about moving from NIAMD [National Institute of Arthritis and Metabolic Diseases] to the Cancer Institute but decided that I would prefer to stay as an independent investigator in the CEB so I stayed when Ira moved. We continued to collaborate until I left in 1971. I think I was just very comfortable in the CEB. I liked the people. I did not see any reason to move if we could continue to work together if we wanted to even if we were in different Institutes, so that's what we did.

JG: You go on to Harvard Medical School. What intrigued you about that opportunity?

RP: Well about that time, 1969 or 1970, I decided I wanted to leave the NIH and began looking at positions elsewhere. I think I probably took the position at Harvard because I was overly attracted by its reputation and the supposed glory of going there. It seemed like an exciting place to be and in comparison to the other places I had looked, this just seemed like the nicest job that I had been offered up until then. Rather than wait for others, I decided to take that.

JG: You were at NIH for about six years?

RP: Six years.

JG: What had changed over those six years? How had NIH changed?

RP: I don't think I was aware of changes other than growth, and that seemed like a good thing. There was a position for me. There were positions for other people. The ambiance and the quality of life here seemed pretty stable. I think as I recall Dr. James Shannon was the NIH Director through that whole period and there weren't significant changes in the upper administration of the NIH so at least from the low level position that I had as a staff scientist I didn't appreciate any changes. Of course there were periodic job freezes and spending freezes and all the things that go with the government but that didn't seem to change over the time that I was there.

JG: Okay, so quickly walk me through the remainder of your career. You eventually return to the University of Chicago?

RP: Yes. I was at Harvard for ten years in the physiology department and I decided when I was leaving NIH that I would leave the world of bacterial genetics and do something more related to physiology and I thought perhaps medicine and began to study chromaffin cells in the adrenal medulla that make and secrete epinephrine or norepinephrine and that is what I then pursued for much of my remaining research career.

I was at Harvard for ten years from 1971 to 1981. I left because I did not get tenure there which was a very difficult transition for me. I won't say it was the first time that I was not able to pursue what I wanted to do, but it was a difficult episode in my life to not get tenure, although I sort of knew objectively all the time I was there that the chances of being promoted were very slim. They promote very few people from untenured to tenured positions but still you always feel that you are the special one that will make it, and so that was hard.

I went to the University of Illinois at Chicago, where I was chairman of the Department of Physiology and Biophysics, and again as I look back there is this sort of swing between being at a very academic environment and going to UIC which was not quite Bellevue but it was a large State institution. Its mandate was both to provide clinical care for poor people in Chicago at the University of Illinois Hospital but we really educated not just physicians but lots of allied health professionals and so it was a much more public service oriented environment. Our responsibility was not just to do research but to educate the people who would be the pharmacists and nurses, allied health people as well as physicians and graduate students, and so there was something, although it was not anywhere near as intellectually or academically exciting as other places I had been, there was a feeling of doing something that was socially responsible and not just the self-indulgence of doing research that I enjoyed doing.

I was at UIC for just over five years and those were very happy years. I was not looking to move but I was offered a position at the University of Chicago and I guess having grown up there and gone to school there and feeling very attached to the institution I decided I would move. I went back to the University of Chicago and that is where I have been for the rest of my academic career. I did retire from the faculty a couple of years ago so now I am Professor Emeritus.

JG: What were some of the interesting projects that you did at the University of Chicago in the twenty years that you spent there?

RP: Well, one of the most important to me personally was that in the early 1990s I served a term as Associate Dean for Biology in the College of the university and so I was responsible for overseeing and organizing all of the undergraduate education in biology. One of the things that I like a lot about the University of Chicago, which is different from many other medical centers, is that the medical school is right on the main campus of the university. It is sort of embedded into the university. We don't really have a separate medical school it is really just a part of what is called the Division of Biological Sciences.

JG: This is unlike Harvard where the medical school—

RP: That's right, that's right. At Harvard there is Cambridge and then there is the medical school in Boston and that is the way many schools are organized. In Chicago there was sort of one faculty who were responsible for all of the education and research in biology, undergraduate, graduate, and medical, so even though my primary appointment was in pediatrics, as I told you, I was very pleased with the undergraduate education that I got. I was a big believer in liberal education and believe that all college students whatever they wanted to do when they grew up should study biology because it was an important part of understanding the world.

I was offered and took this position where I was responsible for undergraduate education and that was a defining moment for me for several reasons because in that position I had to think about what was important to teach undergraduates about biology and that led to the realization that as excited as I was about my own research about the biology of chromaffin cells and how they synthesize and store and secrete these hormones, that was not at all relevant to what you wanted students to learn about biology and I thought what students really needed to learn was the theory of evolution by natural selection and understand how biologists view the world from an evolutionary perspective.

That period really led me to ultimately close my laboratory and begin teaching and doing a little bit of writing on the subject of what is now known as evolutionary medicine or Darwinian medicine which is an integration of evolutionary biology with medicine. That has been my own teaching and intellectual passion for the last five or ten years. That is my personal evolution.

JG: A few more questions if you don't mind?

RP: Oh, sure.

JG: How do we train scientists and researchers? I guess you need to find people that are very creative but then also very skeptical and how do you balance that?

RP: I am not sure I can give an answer to that, so if I can be like Sarah Palin, and answer a different question. What has concerned me a lot about graduate education particularly in medical centers like the University of Chicago or Harvard is that we are really preparing our students, educating them for jobs that don't exist, and for very narrow career opportunities because the kind of research that people do in the major medical centers is so expensive and time consuming it can only be done in medical centers. It can't be done in liberal arts campuses and people become so specialized in their own research that they become, in a sense, too narrowly focused to think about broad areas of biology. This became an issue for me when I was associate dean and trying to get faculty to teach undergraduates. Not only did most faculty not want to do it because it was taking time away from their research, they were unprepared.

JG: It is perceived as a burden.

RP: Right, which one can understand in that environment, but so many of my colleagues who are terrific scientists, and I don't mean this in a disparaging way, had such narrow expertise that they were really uncomfortable teaching in the broad way that you have to teach undergraduates. They were very good at teaching graduate courses in the areas of their expertise, but they became so focused, and particularly the young faculty that had come out of graduate school, or a postdoctoral fellowship, they were super, super scientists in their areas of research but they were not prepared—not only for the real world—but even the sheltered academic world of liberal education and biological education.

I don't see the resolution to this problem because if you're going to be in a medical center it is competitive and time consuming and you have to be focused and specialized. Life seemed to be simpler when I grew up then and you did have time to pursue the sort of broader ideas. I am not saying that because there was anything special about me, but I think it was just the environment at the time that I grew up that it was not as competitive and highly pressured as it is now.

JG: I have read that the dissertation topic becomes very important because it sets your entire career path and that there is a lot of pressure to pick a significant topic.

RP: I think it is terribly hard for graduate students to have any idea what an important problem is and so they choose to go to laboratories where people are perceived as successful in important fields. As I have described my professional life and career to you I have worked in several different areas and I have had the luxury to do that because of the time that I grew up. I do have the feeling now that people are much likely to stay more closely to the field in which they did their graduate work.

JG: And not switch between one area and another?

RP: That's right. I think people who would be getting degrees and studying proteoglycans today are more likely to go onto postdocs in a related area and not wind up studying cyclic AMP and bacteria.

JG: What is the health of the profession today?

RP: Which profession?

JG: Research biology broadly defined?

RP: There is good news and bad news. I think it has been enormously successful and has grown so much that now maybe the field is overpopulated and we are suffering from the problems of overpopulation. I think there is a lot of discouragement among younger people about how hard it is to get grants and get academic positions and establish themselves in an academic career. I think a lot of students are frustrated by that. On the other hand, those people who are successful are doing wonderfully and the science is very exciting. I don't know what the solution to that is either. I think we are the victims of our success that we have educated all these very talented people and we do not have by any means the resources to help them continue. That is why I mentioned the problem about the narrow focus of graduate and post-graduation education that our students in Chicago, and many other places, are educated to do what we do, to be faculty in medical centers and there are very limited positions.

JG: At a Research I Institution?

RP: That's right, exactly right. I think most of our students would see, and most of my colleagues would think, that being a faculty member at a liberal arts college was a sign of failure. You couldn't make it in a Research I Institution. That should not be the mentality, but unfortunately it is, and people don't feel good if they wind up there. But being a faculty member at a liberal arts college is a perfectly fine thing to do and we don't see that.

I mean one of the ways that the world has changed I think is that I did grow up in what is always referred to as the "Golden Age at NIH" or biomedical research when it really was a growing field. There were always new academic positions opening up, new medical schools, or schools enlarging. Of course we always complained about grants but the NIH budget was growing and there were always opportunities to get grants so it was a much easier time in which to develop academic careers and I think it is just much, much harder these days.

JG: How about hobbies in your retirement?

RP: Hobbies? I like to think that I retired from committee meetings and I have not retired from the academic life. I still teach a course a year in evolutionary medicine and for the last ten or fifteen years I have been editing a journal called *Perspectives in Biology and Medicine*, which I continue to do and enjoy. I am writing and hope to write more about this field of evolutionary medicine. It is an interdisciplinary and controversial field because most physicians I think don't see evolutionary biology as relevant to what they do because evolutionary concepts don't immediately impact patient care. I am on a crusade to help physicians understand why thinking from an evolutionary perspective is a good thing to do even if it does not affect how you are going to take care of your patients. I am writing and feel I have a mission. [Laughs] It is something I want to do and so you know between editing and teaching, doing all these things. The nice thing about retiring is that I can do all these at my own pace without feeling responsible to anybody. I have three grandchildren who I like to spend time with and I can do that when I want. Those are what I am doing at this stage of my retirement.

JG: Last question. If you have one piece of advice, one lesson learned that you would like to pass on to a future researcher or scientist working ten or twenty years into the future what would that be?

RP: I think what has impressed me about many good scientists and I think sometimes I have not been as good at this as I wish I were . . . One of the things Ira was very helpful to me with was that you have to have the courage of your convictions and continue to pursue your ideas even if they are unpopular and met with resistance. It is not enough to be smart and creative but there is a certain amount of intellectual courage or personal courage that is required to go against the grain and to maintain that what you are doing is worthwhile and important even when the people around you, your colleagues, members of the study section, the reviewers of journals, think that what you are doing is misguided. I suppose if I were giving advice to the young scientist I would urge them to stick to their guns and maintain their own personal courage in the face of adversity. I guess that is it.

JG: Thank you very much.

RP: It was my pleasure.

[End of Interview]